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TITLE: Early Whole Blood for Patients Requiring Massive Transfusion After Major Trauma

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14. ABSTRACT

The acquired coagulopathy of trauma is responsible for a large percentage of early deaths in civilian trauma practice and is a major cause of battlefield mortality. Widespread recognition has provided a rationale for fundamental changes in the initial management of severely injured patients through prevention of hypothermia, damage control surgery, massive transfusion protocols and early triage to intensive care units for optimized resuscitation. Despite these major advances, hemorrhage remains a leading cause of early death in both civilian trauma and military combat casualty care. However, it is unclear how early whole blood will affect coagulopathy in this cohort of patients as compared to the current standard of care. This study will assess if patients who require massive transfusion can be accurately predicted early after emergency department arrival and assess if the use of stored whole blood during initial resuscitation will reduce transfusion needs compared to transfusion with component therapy and thus improve outcome. Over the last year, the primary clinical project has completed enrollment, randomizing 115 subjects. Additionally, the two ancillary projects are continuing the analysis data collected from subjects in this study to characterize the complement, platelet and immune-inflammatory response after trauma as well as the effect of adiposity after shock and resuscitation in these severely injured patients.

15. SUBJECT TERMS
Whole Blood, Trauma, Transfusion

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Introduction

Severe uncontrollable coagulopathy in major trauma patients continues to be a major factor in trauma mortalities. This proposal will implement a randomized, controlled trial of early whole blood transfusions in high risk, major trauma patients to determine if whole blood can prevent or control severe coagulopathy compared to standard massive transfusion care (currently 1:1 ratio of FFP to PRBC). Second, this proposal will determine if we can accurately predict major trauma patients who will require massive transfusion within 20 minute of arrival to the emergency department. Finally, this study aims to test commonly utilized point of care analysis and determine its reliability in early prediction of transfusion needs. Two connected sub-projects under the leadership of Dr. Charles Wade and Dr. Rosemary Kozar are associated with this project and are further discussed in the text of the report.

Body

Primary Project (Cotton-PI)

The patients are enrolled into this study at the time blood products are ordered by the attending trauma surgeon. Patients will receive either whole blood or component therapy and will be monitored by direct observation for the first six hours after admission. Coagulation profiles will be obtained at 3, 6, 12, and 24 hours after admission. Additional blood samples are drawn for the two sub-projects and will be analyzed separately. All data involving the care of enrolled patients are entered into the Trauma Research Database which is approved by the University of Texas Health Science Center (UTHealth) Committee for the Protection of Human Subjects (CPHS). A research statistician, who will remain blinded to the treatment group, will evaluate the de-identified data for analysis.

AIM 1: In a prospective, randomized trial, evaluate transfusion of stored whole blood and pooled platelets during transfusion therapy.

The randomized trial began enrollment on May 23, 2011 and upon completion of the enrollment period, 1695 patients were screened, 115 were randomized and 78 received study product. 54% were randomized in group A and 46% were randomized in group B. See Figure 1. Additionally, each month the target enrollment goal was met or exceeded. See Figure 2. Over the course of this trial, three data safety and monitoring board meetings were held where no major issues or concerns were raised.

AIM 2: Accurately predict major trauma patients who will require a blood transfusion

We have collected this prospective data on enrolled subjects for this study and it is currently being thoroughly analyzed. This data will be used to assess predictors of massive transfusion and the process (and its limitations) involved in carrying out a study of patients with life-threatening hemorrhage.

AIM 3: Test commonly utilized point-of-care analysis and determine its reliability in early prediction transfusion needs.

International normalized ratio (INR), thromboelastogram (TEG), activated clotting time (ACT), prothrombin (PT) and partial thromboplastin time (PTT) were also collected on enrolled subjects. The analysis of this data is ongoing.

Ancillary Projects

Characterization of Complement, Platelet and Immune-inflammatory Response to Trauma (PI Wade)

Task 1: Blood samples will be collected in 2- and 3-ml citrate vials from severely injured patients upon ED arrival and periodically for up to 5 days at the ICU. Samples will be centrifuged to separate serum and plasma fractions for each sample. Samples will be frozen for future studies of complement proteins and activity, as well as immune-inflammatory biomarker identification and quantification.

205 samples have been collected form 41 patients. Samples were collected at 5 timepoints: 0, 3, 6, 12, and 24 hours. An additional 144 samples, which included day 5 were collected in another 24 patients. The study has focused on the critical first 24 hours of acute resuscitation. These timepoints were chosen in collaboration with Dr. Kozar and Dr. Cotton. Samples were stored until the end of enrollment which was August 2012. At this time, samples were shipped out to collaborator centers where additional tests were conducted. Data analysis is currently on-going.

Task 2: Collection of extensive data on each study subject's demographics, type and degree of injury, and continuous physiologic, metabolic, and biochemical measures as set forth in the original IRB-approved protocol for Dr. Cotton's prime project. In addition, the patient's history before and during hospitalization in the ICU, the occurrence of sepsis, organ failure, systemic inflammatory response syndrome, and other complications of traumatic injury will be captured.

Collection has continued and is proceeding as planned and data is being stored in a centralized database that has de-identified patient information and this will has been and will be available to investigators for data mining and analysis.

Inflammation and Adiposity after Hemorrhagic Shock and Resuscitation (PI Kozar)

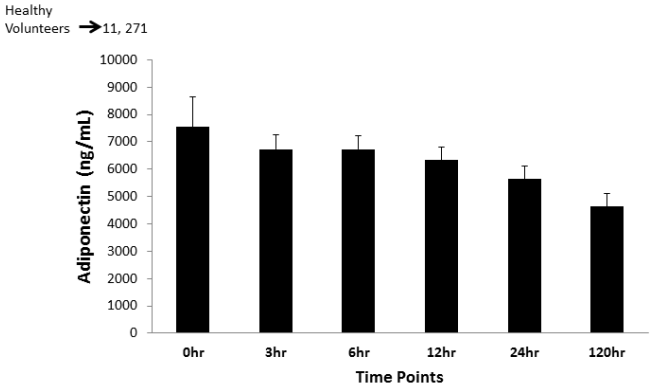
Evaluate sarcopenia based on admission CT and compare to BMI and outcomes.

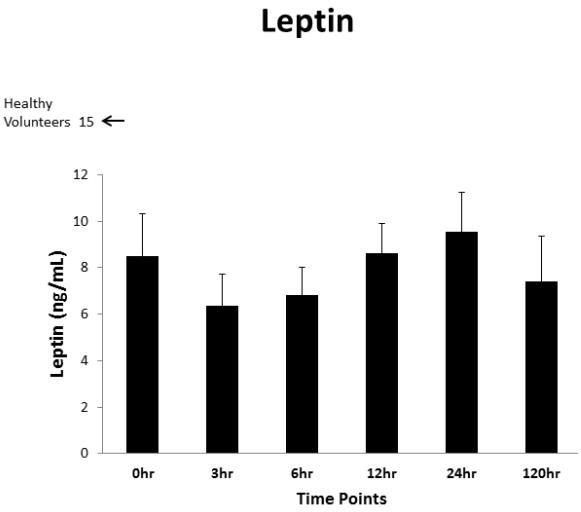
Patients that were admitted to the ICU, on a ventilator, and had an admission CT scan of the abdomen are being saved on CDs and will be sent to our collaborator, Dr. Mourtzakis, for calculation of sarcopenia based on muscle mass at the third lumbar vertebrae. There were 58 patients admitted to the ICU (this excludes deaths < 24 hours and those admitted to the floor or a step down unit). Of the 58 patients, 45 were intubated at least one day. Of the 45 patients that were in the ICU and intubated for at least one day, those with an abdominal CT will serve as the basis for our study. We are in the process of determining which of the 45 patients had an abdominal CT.

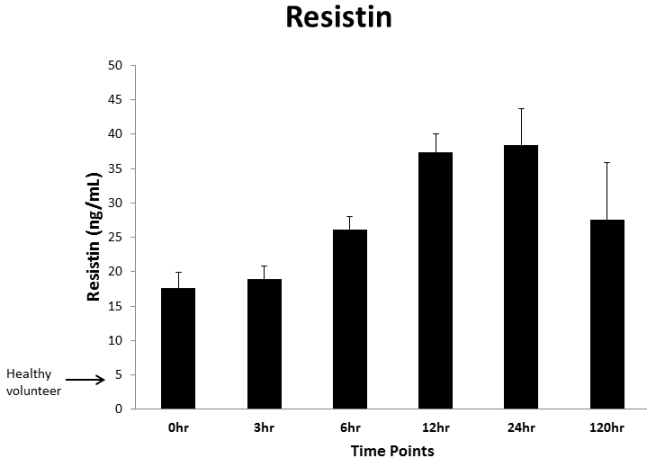
We have just completed a retrospective review of elderly trauma patients and found that sarcopenia, but not BMI, correlated with increased mortality, increased ventilator days and longer ICU stays. This manuscript is under final review by *Critical Care.*

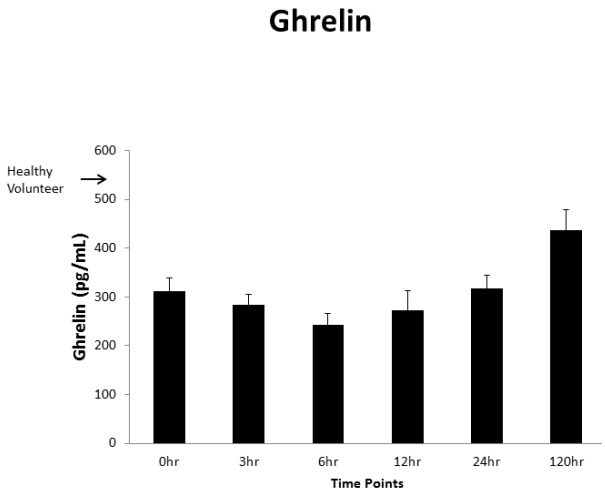
Measure serum (adipokines, leptin, adiponectin, and ghrelin).

We obtained serial samples thru 24 hours on 60 patients and samples thru five days on 23 patients. We measured serum adiponectin, leptin, ghrelin, and resistin, and compared values to normal healthy volunteers. Results are shown below. Statistical analysis of changes over time have not yet been done, but adiponectin, leptin, and ghrelin were all lower than in healthy volunteers at all timepoints. Adiponectin slowly decreased over time; leptin showed no discernible pattern of change over time; while ghrelin slightly increased by day 5. On the other hand, resistin was higher at all timepoints compared to healthy volunteers and increased over time up to day 5.









Determine nutritional adequacy for ICU patients.

In an attempt to correlate serum adipokines with nutritional adequacy, we have thus far focused our efforts on the 23 patients with day 5 labs. Of these 23 patients, 11 were transferred out of the ICU prior to day 5. One was in the ICU but did not receive supplemental nutrition (regular diet only). That left 11 patients to assess nutritional adequacy on, which is defined as total calories and protein received/target total calories and protein x 100.

Nutritional adequacy at day 7 was only 36% (range 20-79%) for calories and 37% for protein. We are still analyzing the overall population, but preliminary results show that caloric adequacy was only 44% and protein was 45%.

Our data suggests that despite having a well-established feeding protocol and a focus on early enteral feeding, these high risk patients are being grossly underfed. Current data suggests that feeding at 85% of goal is optimal. We have not yet performed a statistical analysis to determine if we can correlate mortality with nutritional inadequacy. Our small sample size may limit analysis.

Key Accomplishments

- Screened 1695 patients
- Randomized 115 patients (54% Group A and 46% Group B)
- Completing data analysis
- Drafting initial manuscript to report results from primary study
- 205 samples have been collected for the ancillary immune-inflammatory analysis
- Completed preliminary analysis on 60 serial samples for adipokine assessment
- Obtained preliminary results on nutritional adequacy of eligible ICU patients

Reportable Outcomes

- Maintained all necessary regulatory approvals (Appendix 1)
- Completed clinical trial
- Submitted and Accepted abstract to 133th American Surgical Association Meeting (Appendix 2)
- Manuscript on elderly trauma patients is under review at Critical Care.

Conclusions

This project is proceeding and will continue as planned. Monthly targets were exceeded and enrollment has now been completed. Data analysis for the primary project is nearly completion and the initial manuscript is currently being drafted and will be submitted for peer-review in the Spring of 2013. The sub-projects are also proceeding without incident and are likely to yield a wealth of information. As we have previously reported, we have been able to capture and define those patients, provide and system issues experienced in carrying out a randomized trial of patients with life-threatening bleeding. We have been able to use the experience from this trial to progress forward and with another randomized clinical trial in this severely injured patient population.

References
N/A

Appendices
Appendix 1 – Current Human Use Approval
Appendix 2 – Accepted Abstract to ASA

Supporting Data
Figure 1

Early Whole Blood in Patients requiring Transfusion after Major Trauma (HSC-MS-07-0499)
Recruitment Flow-Chart: May 24, 2011 – August 1, 2012

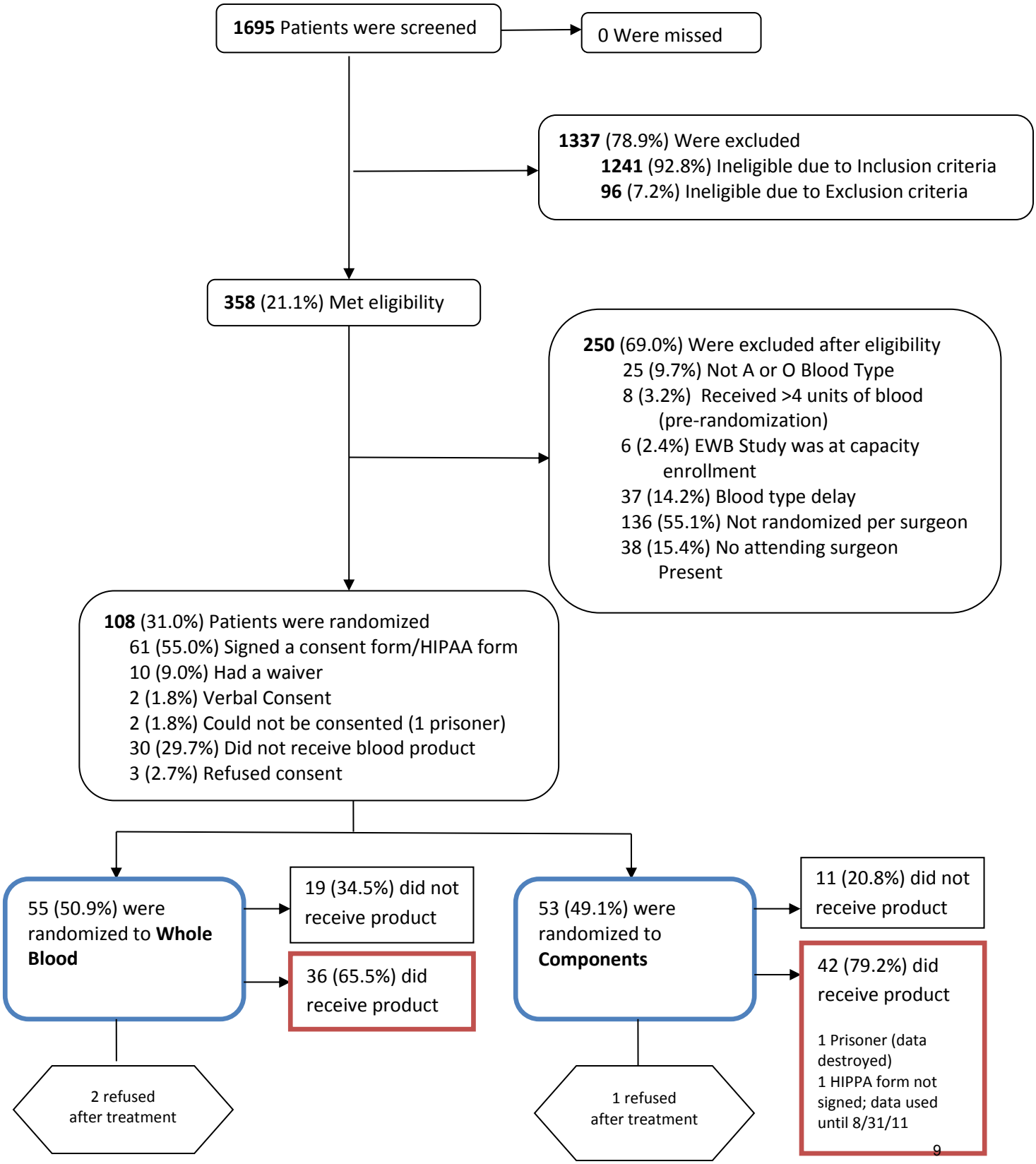
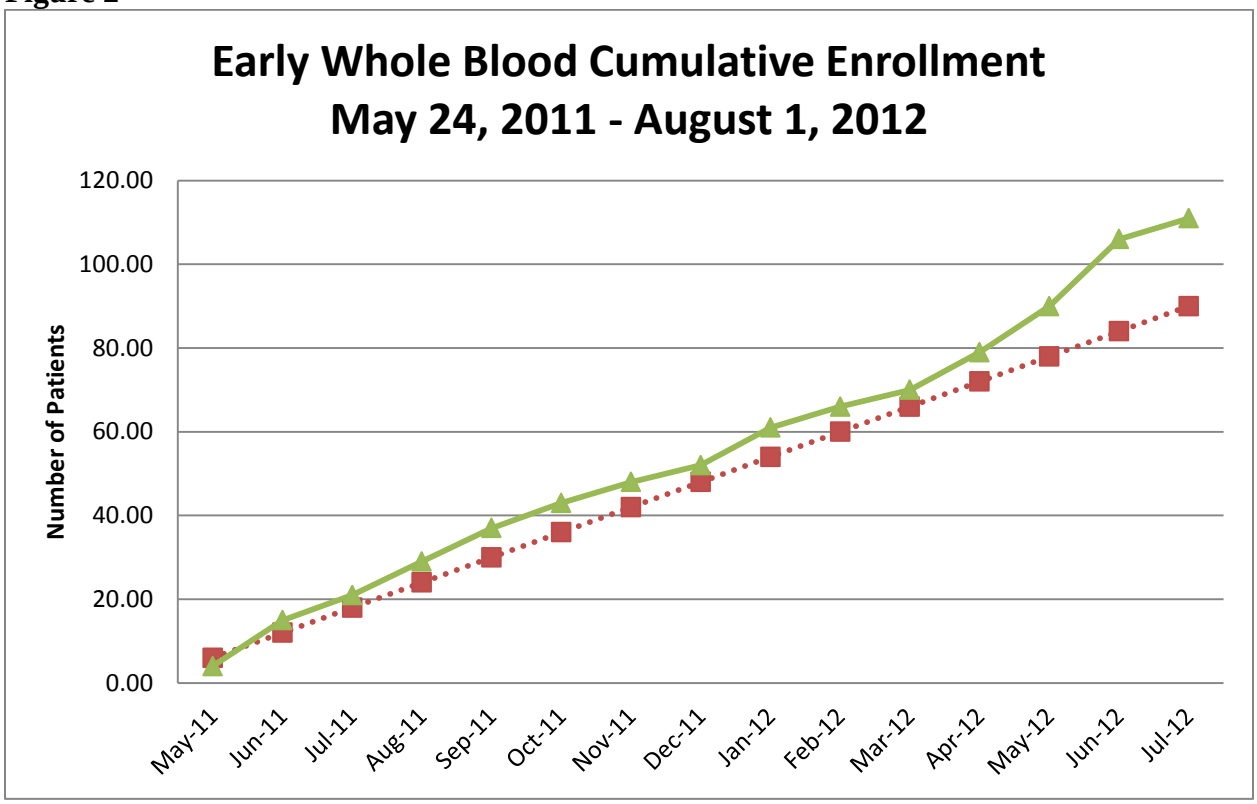


Figure 2


Early Whole Blood Cumulative Enrollment
May 24, 2011 - August 1, 2012
Number of Patients
120.00
100.00
80.00
60.00
40.00
20.00
0.00
May-11
Jun-11
Jul-11
Aug-11
Sep-11
Oct-11
Nov-11
Dec-11
Jan-12
Feb-12
Mar-12
Apr-12
May-12
Jun-12
Jul-12

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NOTICE OF CONTINUING REVIEW APPROVAL January 15, 2013

HSC-MS-07-0499 - *Early Whole Blood IN Patients Requiring Transfusion After Major Trauma*

PI: Bryan Cotton, MD

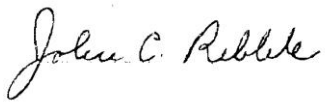
PROVISOS: Unless otherwise noted, this approval relates to the research to be conducted under the above referenced title and/or to any associated materials considered at this meeting, e.g. study documents, informed consents, etc.

NOTE: If this study meets the federal registration requirements and this is an investigator-initiated study, or if the PI is the study sponsor or holds the IND/IDE applicable to this study, and no one else has registered this trial on the national registry, you are required to register this trial on the national registry at www.clinicaltrials.gov in order to publish results in any of the key peer-reviewed journals. For further information write to clinicaltrials@uth.tmc.edu or call 713-500-7909.

APPROVED: By Expedited Review and Approval

REVIEW DATE: January 15, 2013

APPROVAL DATE: January 15, 2013 **EXPIRATION DATE**: 12/31/2013

CHAIRPERSON: John C. Ribble M.D. 

Upon review, the CPHS finds that this research is being conducted in accord with its guidelines and with the methods agreed upon by the principal investigator (PI) and approved by the Committee. This approval, subject to any listed provisions and contingent upon compliance with the following stipulations, will expire as noted above:

CHANGES: The PI must receive approval from the CPHS before initiating any changes, including those required by the sponsor, which would affect human subjects, e.g. changes in methods or procedures, numbers or kinds of human subjects, or revisions to the informed consent document or procedures. The addition of co-investigators must also receive approval from the CPHS. ALL PROTOCOL REVISIONS MUST BE SUBMITTED TO THE SPONSOR OF THE RESEARCH.

INFORMED CONSENT: Informed consent must be obtained by the PI or designee(s), using the format and procedures approved by the CPHS. The PI is responsible to instruct the designee in the methods approved by the CPHS for the consent process. The individual obtaining informed consent must also sign the consent document. Attached is the approved and validated informed consent form. You must discard all previous informed consent documents being used and replace them with this stamped validated version. **Please note that only copies of the**

appropriately dated, stamped approved informed consent form can be used when obtaining consent.

UNANTICIPATED RISK OR HARM, OR ADVERSE DRUG REACTIONS: The PI will immediately inform the CPHS of any unanticipated problems involving risks to subjects or others, of any serious harm to subjects, and of any adverse drug reactions.

RECORDS: The PI will maintain adequate records, including signed consent documents if required, in a manner which ensures subject confidentiality.

Appendix 2 – Accepted Abstract to ASA

A Randomized Controlled Trial of Whole Blood Versus Component Therapy in Severely Injured Patients Requiring Large Volume Transfusions

Objective: To determine if resuscitation of severely injured patients with whole blood results in fewer overall transfusions compared with component therapy

Background: For decades, whole blood (WB) was the primary product for resuscitating patients in hemorrhagic shock. Following dramatic advances in Blood Banking in 1970's, blood donor centers began supplying hospitals with individual components (RBC, plasma, platelets) and removed WB as an available product. However, no studies of efficacy or hemostatic potential were performed prior to doing so.

Methods: Single center, randomized trial of severely injured patients predicted to receive massive transfusion. Pregnant patients, prisoners, those <18 years of age, or >20% TBSA burns were excluded. Patients were randomized to WB (1 U WB+ 1 U platelets) or component, COMP, (1 U RBC+ 1U plasma+ 1U platelets) immediately on arrival. 1U WB= 1U RBC+ 1U plasma. The study was performed under the Exception from Informed Consent (FDA 21 CFR 50.24). Primary outcome was 24-hour transfusion volumes.

Results: 107 patients were randomized (55 WB, 52 COMP) over 14-months. There were no differences in demographics, arrival vitals or labs, injury severity or mechanism. Transfusions were between groups. However, when excluding severe brain injury patients, WB group received less 24-hour RBC (median 3 vs 6, p=0.02), plasma (4 vs. 6, p=0.02), platelets (0 vs. 3, p=0.09) and total products (11 vs 16, p=0.02). Linear regression confirmed these findings ($p<0.05$).

Conclusion: Compared to COMP therapy, WB did not reduce transfusion volumes in severely injured patients predicted to receive massive transfusion. However, in patients without severe brain injuries, WB significantly reduced transfusion volumes.